for 10 months in a tightly capped amber bottle was found to contain approximately 50% MTX). Although the longer chain monoesters are much more stable than the methyl derivatives, they should be stored at low temperature, preferably in a desiccator, and their homogeneity should be checked periodically by TLC.

(23) G. E. Foley and H. Lazarus, *Biochem. Pharmacol.*, **16**, 659 (1967).
(24) S. P. Rothenberg, *Anal. Biochem.*, **16**, 176 (1966).
(25) B. T. Kaufman, *Methods Enzymol.*, **34**, 272 (1974).

Effects of Molecular Modification on Hypocholesteremic Activity of 1,3-Bis(substituted phenoxy)-2-propanones and Related Derivatives

Steven D. Wyrick* and C. Piantadosi

Division of Medicinal Chemistry, School of Pharmacy, The University of North Carolina, Chapel Hill, North Carolina 27514.
Received May 2, 1977

A series of 1,3-bis(substituted phenoxy)-2-propanones, long-chain ketones, and related derivatives has been synthesized, and it has been found that certain analogues produce significant lowering of serum cholesterol levels in Sprague–Dawley rats. These compounds possess no estrogenic properties and are nontoxic at 10 mg/kg/day. Physical studies on these compounds include an attempt to correlate hypocholesteremic activity with the lipophilic, electronic, and steric properties of the compounds. The 1-octanol–H_2O partition coefficient was measured for certain derivatives and the π constant for the substituents was calculated. Hammett's σ constants for aromatic substituents were obtained from the literature. The only correlation found to exist is between hypocholesteremic activity and steric size and position of the aromatic substituents in the propanones.

Previous work has revealed that certain analogues of a series of 1,3-bis(substituted phenoxy)-2-propanones[1] and long-chain ketones[2] possess excellent hypocholesteremic activity at dose levels of 10 mg/kg/day. Both series of compounds are nontoxic and nonestrogenic, possessing none of the antifertility properties seen in the 2,8-dibenzylcyclooctanones.[3] The most probable hypocholesteremic mechanism lies in the inhibition of HMG-CoA reductase by 1,3-bis(*p*-methylphenoxy)-2-propanone and 2-hexadecanone, while 2-hexadecanone also inhibits acetyl-CoA synthetase.[4] 1,3-Bis(*p*-methylphenoxy)-2-propanone has also been shown to produce significant lowering of serum triglyceride levels at 10 mg/kg/day in correlation with the inhibition of *sn*-glycerol-3-phosphate acyltransferase and phosphatidate phosphohydrolase in vitro.[5] The work reported here extends the propanone series in order to elucidate more completely the effects of molecular modification on hypocholesteremic activity.

Experimental Section

Chemical Synthesis. All melting points were corrected and obtained using a Thomas-Hoover melting point apparatus. Purity of intermediates not subjected to elemental analysis was ascertained by thin-layer chromatography. Micro-thin-layer chromatography was performed using silica gel G coated microslides with chloroform as the eluting solvent. All column chromatography was performed using either silica gel 60 (70–230 mesh) or Florisil. Infrared spectra were obtained on a Perkin-Elmer 257 infrared spectrophotometer. All chemicals were used as received from manufacturers. Elemental analyses (±0.4%) were performed on all biologically tested derivatives by either Atlantic Microlab, Atlanta, Ga., or M-H-W Laboratories, Garden City, Mich. Infrared spectral data are included for those oils only that were column chromatographed and, therefore, not identified by their respective boiling points.

General Procedure for Preparation of 1-(Substituted phenoxy)-2-propanols 1 and 2. One equivalent each of the appropriate phenol and sodium hydroxide was dissolved in 1,4-dioxane (30 mL per 0.3 mol of phenol) at 98–101 °C. To this solution was added 1.0 equiv of propylene oxide dropwise over a 10-min period, and the reaction mixture was stirred for at least 5 h. The 1,4-dioxane was removed in vacuo and the residue dissolved in ether, extracted with 10% sodium hydroxide, and dried over Na_2SO_4. Filtration and removal of the ether afforded the crude product which was purified by either distillation or column chromatography (Table I).

General Procedure for Preparation of 1,3-Bis(substituted aryloxy)-2-propanols 3–6. These derivatives, except **28**, were prepared according to the general procedure for the preparation of 1,3-bis(substituted phenoxy)-2-propanols[1] (Table I).

General Procedure for Preparation of 1-(Substituted phenoxy)-3-(substituted benzoxy)-2-propanols 7 and 8. Dry pyridine (50 mL) and 0.10 mol of the appropriate 3-(substituted phenoxy)-1,2-propandiol were dissolved in 400 mL of dry chloroform, and the solution was cooled to 0 °C. To this solution was added dropwise 0.10 mol of the appropriate benzoyl chloride at 0 °C with stirring over a 1-h period. After the addition, the reaction temperature was allowed to slowly come to room temperature and was stirred an additional 3 h. The chloroform and pyridine were removed in vacuo, and the residue was dissolved in sufficient ether and extracted with water (1 × 150 mL), 1.0 N H_2SO_4 (3 × 150 mL), water (1 × 150 mL), 5% $NaHCO_3$ (3 × 100 mL), and water (1 × 100 mL). The ether solution was dried over Na_2SO_4 and filtered, and the ether was removed to afford the crude ester which was then purified by chromatography or recrystallization (Table I).

General Oxidation Procedure for 9–23. All ketones reported in this paper (except **35** and **36**) were obtained from the corresponding hydroxy derivatives using dicyclohexylcarbodimide (DCC), dimethyl sulfoxide (Me_2SO), pyridine, and trifluoroacetic acid as previously described[1] (Table II).

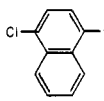
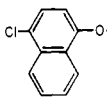
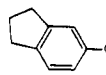
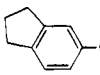
1-(*p*-Methylphenoxy)-2-hexadecanol (24). *p*-Cresol (10.1 g, 0.093 mol) and 3.7 g (0.093 mol) of NaOH were dissolved in 40 mL of 1,4-dioxane at 90–95 °C. To this solution was added 15.0 g (0.062 mol) of 1,2-epoxyhexadecane dropwise, and the reaction was stirred at 100 °C for 4 h. The dioxane was removed in vacuo, the residue was taken up in 400 mL of chloroform, extracted with water (2 × 100 mL) and 10% NaOH, dried over Na_2SO_4, and filtered, and the chloroform was removed to give a crude, brown solid. Recrystallization from 2-propanol afforded 15.7 g (73%) of crystals: mp 86–88 °C; R_f 0.68.

1-(*p*-Methylphenoxy)-2,3-epoxypropane (25). The general procedure for the synthesis of phenoxypropylene oxides described by Britton and Slagh was followed.[6] Sodium hydroxide (7.4 g, 0.185 mol) and 20.0 g (0.185 mol) of *p*-cresol were dissolved in 50 mL of water at 98–100 °C. To this solution was added 34.2 g (0.369 mol) of epichlorohydrin, and the reaction was stirred overnight. The solvents were removed in vacuo, the residue was taken up in ether, extracted with water (2 × 100 mL), dried over Na_2SO_4, and filtered, and the ether was removed to give 42.1 g

0022-2623/78/1821-0386$01.00/0

Table I. 1-Substituted and 1,3-Disubstituted 2-Propanols

$$RCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2R'$$

No.	R	R'	Mp or bp (mm), °C, or IR data (cm^{-1})	R_f	% yield	Formula	Recrystn solvent
1	4-CH_3-C_6H_4-O-	H-	71–74 (0.03)	0.4	78	$C_{10}H_{16}O_2$	Distilled
2	4-NO_2-C_6H_4-O-	H-	Oil; ν_{OH} 3420, ν_{arom} 1600–1610, ν_{CO} 1060	0.36	86	$C_9H_{11}NO_4$	Benzene–ether (8:2, 6:4)[a]
3			50–51	0.36	90	$C_{23}H_{20}Cl_2O_3$	2-Propanol
4	C_6H_5-C_6H_4-O-	C_6H_5-C_6H_4-O-	120–127 (crude)	0.4	72 (crude)	$C_{27}H_{24}O_3$	2-Propanol
5	3-OCH_3-C_6H_4-O-	3-OCH_3-C_6H_4-O-	Oil; ν_{OH} 3380, ν_{arom} 1600–1610, ν_{CO} 1060	0.42	23 (crude)	$C_{17}H_{20}O_5$	Benzene, benzene–ether (9:1, 8:2)[a]
6			82–83	0.45	53 (crude)	$C_{21}H_{26}O_3$	2-Propanol
7	2-CH_3-C_6H_4-O-	4-Cl-C_6H_4-C(=O)O-	Oil; ν_{OH} 3450, ν_{arom} 1600, $\nu_{C=O}$ 1725	0.36	77	$C_{17}H_{17}O_4Cl$	$CHCl_3$, $CHCl_3$–ether (6:4, 1:1)[a]
8	4-CH_3-C_6H_4-O-	4-NO_2-C_6H_4-C(=O)O-	106–107	0.3	40	$C_{17}H_{17}O_6N$	Benzene–2-propanol (5:1)

[a] Eluting solvent system used for column chromatography.

of crude oil. Fractional distillation of this oil [75 °C (0.07 mm)] afforded 22.5 g (74%) of product as a colorless oil. Anal. ($C_{10}H_{12}O_2$) C, H.

1-(*p*-Methylphenoxy)-3-octadecyloxy-2-propanol (26). Potassium metal (2.4 g, 0.061 mol) was granulated in 30 mL of dry *p*-xylene at 110–120 °C. To this suspension was added 16.5 g (0.061 mol) of 1-octadecanol in 20 mL of *p*-xylene, dropwise over a 10-min period. The reaction was stirred overnight at 110–120 °C, at which time all of the 1-octadecanol had reacted with the potassium to give a solution. To this solution was added 10.0 g (0.061 mol) of **25** neat dropwise over a 10-min period, and the reaction was stirred overnight at 110–120 °C. The *p*-xylene was removed in vacuo, the residue was taken up in 50 mL of benzene and suction filtered, and the benzene was removed to give 36.1 g of a crude, brown gum which was chromatographed on a column of silica gel (CCl_4–ether, 9:1, 8:2) to give 11.9 g (45%) of product: mp 44–46 °C; R_f 0.6.

1-(*p*-Nitrophenoxy)-2,3-epoxypropane (27). Sodium hydroxide (5.8 g, 0.144 mol) and 20.0 g (0.144 mol) of *p*-nitrophenol were reacted in a manner analogous to the preparation of **25**. Recrystallization from 2-propanol afforded 18.6 g (66%) of product: mp 63–67 °C; R_f 0.62.

1,3-Bis(*p*-nitrophenoxy)-2-propanol (28). Sodium hydroxide (5.7 g, 0.143 mol) and 19.8 g (0.143 mol) of *p*-nitrophenol were dissolved in 75 mL of 1,4-dioxane at 90–95 °C. To this solution was added dropwise a solution of 18.6 g (0.095 mol) of **27** in 30 mL of 1,4-dioxane, and the reaction was then stirred for 24 h at 90–95 °C. The dioxane was removed in vacuo, and the crude brown solid was taken up in 400 mL of chloroform, extracted with water (2 × 100 mL), and dried over Na_2SO_4. Filtration and removal of the chloroform in vacuo afforded a crude, dark solid material. Trituration afforded 19.8 g (62%) of product: mp 134–136 °C; R_f 0.3.

1-(*p*-Nitrophenoxy)-3-chloro-2-propanol (29). Sodium hydroxide (5.6 g, 0.140 mol) and *p*-nitrophenol (30.0 g, 0.216 mol) were reacted in 70 mL of 1,4-dioxane at 98–100 °C to form a suspension of the phenoxide salt. To this suspension was added dropwise 11.2 g (0.121 mol) of epichlorohydrin with stirring over a 10-min period. The reaction was then stirred at 98–100 °C for 24 h. The dioxane was removed in vacuo to give 36.7 g of a crude oil. This material was column chromatographed on silica gel (chloroform, chloroform–ether, 9:1, 8:2, 7:3) to afford 19.1 g (69%) of product as a light yellow oil: IR ν_{OH} 3420, ν_{arom} 1600–1610, ν_{CO} 1050 cm^{-1}; R_f 0.35.

1-Naphthyloxy-3-chloro-2-propanol (30).[7] Epichlorohydrin (48.3 g, 0.52 mol) and 25.0 g (0.173 mol) of 1-naphthol were reacted at 100 °C in the presence of 0.34 mL of piperidine for 4–6 h. The epichlorohydrin was removed in vacuo, and the residue was dissolved in chloroform, washed with excess concentrated HCl and then water, and dried over Na_2SO_4. Filtration and removal of the chloroform afforded a dark, reddish oil which was distilled [158 °C (0.1 mm)] to give 41 g (99%) of product: R_f 0.45.

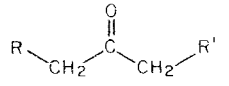
1,3-Dipentoxy-2-propanol (31). Pentanol (36.0 g, 0.41 mol), 1,2-epoxy-3-pentoxypropane[8] (25.0 g, 0.2 mol), and five drops of $HClO_4$ were refluxed for 4 h at 100 °C. The reaction was allowed to come to room temperature and was left overnight. The reaction mixture was dissolved in 200 mL of ether, extracted with water (1 × 50 mL), 10% NaOH (1 × 25 mL), and water (1 × 50 mL), and dried over K_2CO_3. Filtration and removal of the ether afforded an oily residue which was distilled [125–130 °C (2.0 mm)] to give 29.0 g (63%) of product as a colorless oil: R_f 0.68.

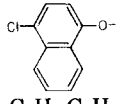
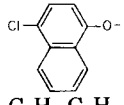
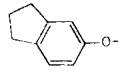
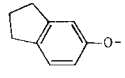
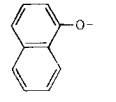
1-(*p*-Methylphenoxy)-3-cyano-2-propanol (32). A solution of KCN (16.0 g, 0.246 mol) in 25.0 mL of water was added to a solution of 40.0 g (0.20 mol) of 1-(*p*-methylphenoxy)-3-chloro-2-propanol[7] in 500 mL of methanol and refluxed for 4 h. The reaction mixture was then concentrated to about one-half its original volume, 250 mL of water was added, and the mixture was neutralized with glacial acetic acid. The mixture was then extracted with 400 mL of chloroform and the chloroform extract dried over Na_2SO_4. Filtration and removal of the chloroform in vacuo afforded a viscous oil. This crude product was crystallized from ligroine–ethyl acetate to afford 23.0 g (60%) of nitrile: mp 57–58 °C; R_f 0.3.

Ethyl 4-(*p*-Methylphenoxy)-3-hydroxybutyrate (33). The above nitrile **32** (23.0 g, 0.12 mol) was dissolved in 250 mL of absolute ethanol, saturated with hydrogen chloride, and refluxed for 5 h. After dilution with water, the mixture was extracted with 250 mL of chloroform, and the chloroform layer was washed with 50 mL of water and dried over $MgSO_4$. Filtration and removal of the chloroform afforded a viscous oil which was distilled [155–160 °C (3.0 mm)] to give 23.0 g (81%) of hydroxy ester: R_f 0.42.

1,3-Bis(2-chloro-4,5-dimethylphenoxy)-2-propanone Diethyl Ketal (34). 1,3-Bis(2-chloro-4,5-dimethylphenoxy)-2-propanone (3.0 g, 0.008 mol) was suspended in a solution of 30 mL of triethyl orthoformate and 20 mL of absolute ethanol. Solution was obtained after addition of 12 drops of concentrated H_2SO_4. After standing overnight at room temperature, TLC showed complete reaction. The solvents were removed in vacuo, the oily residue was taken up in 200 mL of ether and extracted with water (1 × 100 mL), 5% $NaHCO_3$ (2 × 100 mL), and again with water (1 × 100 mL), and the ether solution was dried over

Table II. Products Obtained by Oxidation of the Corresponding Hydroxy Derivatives



No.	R	R'	Mp or bp (mm), °C, IR data	% yield	Formula	Recrystn solvent	Analyses
9	4-CH_3-C_6H_4-O-	H-	Oil; $\nu_{C=O}$ 1725, ν_{arom} 1600–1610, ν_{CO} 1050	52	$C_{10}H_{14}O_2$	Benzene, benzene–ether (9:1)[a]	C, H
10	4-$NO_2C_6H_4$-O-	H-	Oil; $\nu_{C=O}$ 1720, ν_{arom} 1600–1610, ν_{CO} 1060	25	$C_9H_9NO_4$	Benzene, benzene–ether (7:3)[a]	C, H, N
11			58–59	4	$C_{23}H_{18}Cl_2O_3$	2-Propanol	C, H, Cl
12	C_6H_5-C_6H_4-O-	C_6H_5-C_6H_4-O-	170–172	15	$C_{27}H_{22}O_3$	2-Propanol	C, H
13	3-OCH_3-C_6H_4-O-	3-OCH_3-C_6H_4-O-	58–59	42	$C_{17}H_{18}O_5$	2-Propanol	C, H
14			93–95	82	$C_{21}H_{24}O_3$	2-Propanol	C, H
15	4-CH_3-C_6H_4-O-	$CH_3(CH_2)_{12}$-	53–55	86	$C_{23}H_{38}O_2$	2-Propanol	C, H
16	4-CH_3-C_6H_4-O-	$CH_3(CH_2)_{17}O$-	47–49	42	$C_{28}H_{48}O_3$	2-Propanol	C, H
17	2-CH_3-C_6H_4-O-	4-Cl-C_6H_4-C(=O)O-	128–130	78	$C_{17}H_{17}ClO_4$	Benzene–hexane (5:1)	C, H, Cl
18	4-NO_2-C_6H_4-O-	4-NO_2-C_6H_4-O-	173–175	51	$C_{15}H_{12}N_2O_7$	2-Propanol (trituration)	C, H, N
19	4-NO_2-C_6H_4-O-	Cl-	99–101	26	$C_9H_8ClNO_4$	2-Propanol	C, N; H[b]
20		Cl-	119–120	75	$C_{13}H_{11}ClO_2$	2-Propanol	C, H, Cl
21	$CH_3(CH_2)_4O$-	$CH_3(CH_2)_4O$-	Oil; 110–115 (1.0)	40	$C_{13}H_{26}O_3$	Distillation and chromatography (chloroform)[a]	C, H
22	4-$CH_3C_6H_4$-O-	$H_5C_2OC(=O)$-	Oil; $\nu_{C=O}$ 1720–1740, ν_{arom} 1580–1605, ν_{CO} 1040	34	$C_{13}H_{16}O_4$	Distillation and chromatography (benzene, benzene–$CHCl_3$, 95:5, 9:1)[a]	C, H
23	4-CH_3-C_6H_4-O-	4-NO_2-C_6H_4-C(=O)O-	129–132	70	$C_{17}H_{15}NO_6$	2-Propanol	

[a] Eluting solvent system used for column chromatography. [b] H: calcd, 3.51; found, 3.98.

Na_2SO_4. Filtration and removal of the ether in vacuo left 4.2 g of oil which was chromatographed on a column of silica gel (benzene, benzene–ether, 95:5) to yield 3.3 g (93%) of ketal as a colorless viscous oil: IR ν_{arom} 1590, ν_{CO} 1100 cm^{-1}. Anal. ($C_{23}H_{30}Cl_2O_4$) C, H, Cl.

2,4-Dibromo-3-pentanone (35). The synthesis of this compound has been described by Rappe and Schatte.[9]

2,4-Bis(*p*-methylphenoxy)-3-pentanone (36). *p*-Cresol (33.2 g, 0.31 mol) and NaOH (12.4 g, 0.31 mol) were dissolved in 30 mL of 1,4-dioxane at 90–95 °C. To this solution was added dropwise 30.0 g (0.123 mol) of **35** at 100 °C for 1 h. The solvent was removed in vacuo, and the residue was taken up in ether, extracted with water (2 × 100 mL) and 10% NaOH (2 × 50 mL), and dried over Na_2SO_4. Filtration and removal of the ether in vacuo afforded 17.0 g of crude oil. Distillation [81 °C (2.5 mm)] afforded 10.0 g of slightly impure product which was column chromatographed on Florisil (benzene) to give 7.5 g (20%) of product as a colorless oil. Anal. ($C_{19}H_{22}O_3$) C, H.

1-(*p*-Methylphenoxy)-2,3-propanediol (37). *p*-Cresol (22.1 g, 0.204 mol) and 8.2 g (0.204 mol) of NaOH were dissolved in 30 mL of 1,4-dioxane at 90–92 °C. To this solution was added dropwise 15.0 g (0.136 mol) of 3-chloro-1,2-propanediol with stirring over a 10-min period. The reaction was then stirred at 90–92 °C for 3.5 h. The dioxane was removed in vacuo to leave a dark brown semisolid. This crude material was dissolved in 250 mL of chloroform, extracted with water (2 × 100 mL), 10% NaOH (2 × 50 mL), and water (1 × 100 mL), and dried over Na_2SO_4. Filtration and removal of the chloroform afforded 25.8 g (104%) of material as a semisolid: R_f 0.23.

1-(*p*-Methylphenoxy)-2,2-dimethoxy-3-(*p*-nitrobenzoxy)propane (38). Dissolution of **23** (13.2 g, 0.04 mol, Table II) was achieved using 80 mL of methanol and 130 mL of trimethyl orthoformate with warming. Concentrated H_2SO_4 (0.75 mL) was added to this solution and the reaction was allowed to stand overnight at room temperature. The acid was neutralized by the addition of K_2CO_3, the solution was filtered, and the solvents were removed in vacuo. The residue was dissolved in 400 mL of ether, extracted with water (1 × 100 mL), 5% $NaHCO_3$ (1 × 100 mL), and water (1 × 100 mL), and dried over Na_2SO_4. Filtration and removal of the ether afforded 14.3 g (95%) of product as a light yellow semisolid at 25 °C: R_f 0.45.

1-(*p*-Methylphenoxy)-2,2-dimethoxy-3-hydroxypropane (39). The above ketal ester **38** (14.3 g, 0.038 mol) was dissolved in 300 mL of methanol containing 30 mL of 4.0 N aqueous NaOH and the reaction was stirred at room temperature for 1 h, at which time the methanol was removed in vacuo and the residue taken up in 400 mL of ether. The ether solution was extracted with water (3 × 100 mL) and dried over Na_2SO_4. Filtration and removal of the ether afforded 7.1 g (81%) of a saponified hydroxy compound as a yellow oil: IR ν_{OH} 3450, ν_{arom} 1600–1610, ν_{CO} 1090 cm^{-1}; R_f 0.37.

1-(*p*-Methylphenoxy)-3-hydroxy-2-propanone (40). The above ketal **39** (2.0 g, 0.0087 mol) was stirred for 4 h with 15 mL of acetone and 25 mL of 5 N HCl at room temperature. The product precipitated and was extracted with chloroform. The chloroform was removed in vacuo and the solid residue recrystallized from 25 mL of 1,4-dioxane to afford 600 mg (38%) of product as colorless needles: mp 125–128 °C. Anal. ($C_{10}H_{12}O_3$) C, H.

α-(Methylsulfonyl)tridecyl Acetate (41). Methylsulfinylmethyltridecyl ketone[2] (10.0 g, 0.0347 mol) was dissolved in 100 mL of glacial acetic acid, and 25 mL of 30% H_2O_2 was added dropwise. The reaction was allowed to stand overnight at room temperature and the product was precipitated by the addition of 250 mL of water at 10 °C. The product was filtered and washed on the filter with cold water. Recrystallization from 50 mL of 2-propanol gave 5.1 g (46%) of product as colorless needles: mp 49–51 °C. Anal. ($C_{16}H_{32}O_4S$) C, H, S.

Determination of Partition Coefficient. The log *P* measurements for the series were carried out according to the procedure of Hansch.[10,11] Approximately 20.0-mg samples were used for each partitioning, and quantitative measurements were performed using a Cary 15 UV spectrophotometer.

Biological Methods. Sprague–Dawley rats (Zivic Miller, Allison Park, Pa.) were fed Purina lab chow with water ad libitum for the duration of the experiment. Each test compound was suspended in 1% carboxymethylcellulose (CMC)–H_2O and homogenized. Doses (mg/kg) were calculated based on weekly weights of rats. Eight animals were used per assay group. All drugs (10 mg/kg/day) were administered to male rats by an oral intubation needle (0.2 cm^3) daily at 11:00 a.m. Twenty-four hours after the last dose, blood was collected by tail vein bleeding. Nonhemolyzed samples (30 μL) were analyzed for serum cholesterol by a modification of the Liebermann–Burchard method[1,12] (Table III).

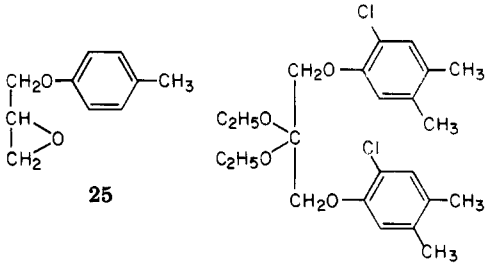
Table III. Percent of Control of Serum Cholesterol after Administration of 10 mg/kg/day of Test Compound Orally to Sprague–Dawley Rats

No.	Days dosed: 4th, $\bar{x}$ ± SD	10th, $\bar{x}$ ± SD	16th, $\bar{x}$ ± SD
Control	100 ± 8	100 ± 10	100 ± 9
Clofibrate	111 ± 16	98 ± 21	106 ± 9
9	111 ± 14	91 ± 5	85 ± 12[c]
10	108 ± 9	108 ± 6	103 ± 7
11	104 ± 6	97 ± 10	94 ± 6
12	116 ± 11	87 ± 9	98 ± 6
13	103 ± 6	84 ± 11	78 ± 13[a]
14	102 ± 10	79 ± 8[a]	75 ± 8[a]
15	95 ± 9	86 ± 7[c]	82 ± 8[c]
16	85 ± 8[c]	83 ± 6[c]	75 ± 5[a]
17	110 ± 7	96 ± 8	110 ± 9
18	103 ± 13	92 ± 6	104 ± 7
19	*d*	*d*	*d*
20	101 ± 5	95 ± 6	75 ± 11[a]
21	103 ± 4	92 ± 9	79 ± 5[a]
22	100 ± 8	101 ± 6	82 ± 12[c]
25	128 ± 14	81 ± 11	73 ± 6[a]
34	128 ± 13	82 ± 6[b]	77 ± 7[a]
36	108 ± 9	102 ± 6	113 ± 7
40	91 ± 7	78 ± 4[a]	107 ± 4
41	93 ± 9	68 ± 8[a]	102 ± 7

[a] $p = 0.001$. [b] $p = 0.010$. [c] $p = 0.025$. [d] Lethal at test dose.

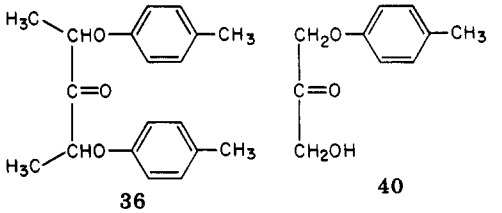
Results and Discussion

The effects of molecular modification on the hypocholesteremic activity of the 1,3-bis(substituted phenoxy)-2-propanones have previously been described. An extension of these studies has been completed in this paper. The diethyl ketal **34** of 1,3-bis(2-chloro-4,5-dimethylphenoxy)-2-propanone[1] was found to be less active than the parent ketone but showed progressively greater activity as time proceeded and may have approached the ketone in activity in a longer dosing period. This may be due to in vivo hydrolysis of the ketal **34** to the ketone. The epoxypropanone derivative **25** was found to be moderately active.



25

34



36 **40**

Substitution of an ester linkage for one of the aryl–alkyl ethers of the propanone series, **17**, produced in inactive compound. Methyl substitution in the α and α' positions, **36**, of 1,3-bis(*p*-methylphenoxy)-2-propanone, an active compound,[1] abolished activity.

Replacement of the aromatic rings with aliphatic chains resulted in an inactive compound,[1] as also evidenced by **21**.

The mixed aromatic–aliphatic derivative **16** showed moderate hypocholesteremic activity. The octadecyl chain in **16** may act as a lipophillic carrier moiety. In order to examine the effect on activity of increasing the size of the aromatic portion of the molecule available for receptor interaction, the bis(naphthyl) and bis(biphenyl) derivatives were prepared and tested. Both compounds were inactive. When various monoaromatic derivatives were tested for activity, none were very active as hypocholesteremics (**9**, **10**, **15**, **19**, **20**, **22**, and **40**).

An attempt was made to investigate any correlation between the pharmacological activity of the series of 1,3-bis(substituted phenoxy)-2-propanones and the lipophilic, electronic, and steric parameters in combination of the substituents on the aromatic ring. A measure of the lipophilic character of a molecule is best expressed as the log of its 1-octanol–water partition coefficient (log *P*). It has been shown that the ability of a drug molecule to cross cell membranes and to ultimately reach its site of action in the biophase is directly related to the drug's log *P*.[13]

Hammett has compounded tables of σ constants for various aromatic substituents and these tables have later been made more complete.[14] These constants were taken as a measure of the electronic properties of the substituents on the phenoxypropanones.

The results from the partition coefficient studies reveal that there is no real correlation between lipophilic (log *P*) and hypocholesteremic activity, since the active compounds have log *P* values ranging from 2.69 to 3.63. Also, several inactive as well as slightly active compounds were found to have log *P* values within this range. The parent unsubstituted compound, 1,3-diphenoxy-2-propanone, and the *o*-methoxy derivative are inactive and slightly active, respectively, and have log *P* values below 2.69. The only assumption that can be made with regard to lipophilicity is that if necessary steric and electronic requirements (if they exist) are met, then a log *P* at least 2.5 is beneficial for activity.

No correlation is seen between the electronic properties of the substituents on the derivatives and biological activity. With respect to the Hammett σ values for the various substituents, both positive and negative valued substituents lend activity to the molecule.

The only real correlation that can be seen with this series is with the steric size of substituents and the position on the ring. As described previously,[1] para-substituted compounds are more active than ortho substituted which are more active than meta substituted, with activity decreasing as the size of the para substituent increases. It is possible that the parent compound, 1,3-diphenoxy-2-propanone, is metablized to the *p*-hydroxy derivative and quickly eliminated in vivo before producing its biological response. Therefore, para substitution would prevent or delay this metabolism, delay elimination, and increase activity as long as the size of the substituent did not prevent receptor interaction.

Acknowledgment. This investigation was supported by Research Grant HL16464-02 from the Division of Heart and Vascular Disease, National Heart and Lung Institute, National Institutes of Health, and in part by Trainee Grant 5T01-GM01770 from the National Institute of General Medical Sciences, National Institutes of Health.

References and Notes

(1) C. Piantadosi, I. H. Hall, S. D. Wyrick, and K. S. Ishaq, *J. Med. Chem.*, **19**, 222 (1976).
(2) S. D. Wyrick, I. H. Hall, C. Piantadosi, and C. R. Fenske, *J. Med. Chem.*, **19**, 219 (1976).
(3) C. Piantadosi, I. H. Hall, J. L. Irvine, and G. L. Carlson, *J. Med. Chem.*, **16**, 770 (1973).
(4) I. H. Hall and G. Carlson, *J. Med. Chem.*, **19**, 1257 (1976).
(5) R. G. Lamb, S. D. Wyrick, and C. Piantadosi, *Atherosclerosis*, **27**, 147 (1977).
(6) E. C. Britton and H. R. Slagh, U.S. Patent 2 371 500.
(7) O. Stephenson, *J. Chem. Soc.*, 1571 (1954).
(8) E. Zielinska and D. Gasztych, *Rocz. Chem.*, **49**, 1405 (1975).
(9) C. Rappe and L. Schatte, *Acta Chem. Scand.*, **16**, 2060 (1962).
(10) T. Fujita, and J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).
(11) C. Hansch, A. Leo, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
(12) A. T. Ness, J. V. Pastewka, and A. C. Placock, *Clin. Chem. Acta*, **10**, 229 (1964).
(13) C. Hansch in "Drug Design", Vol. I, E. J. Ariens, Ed., Academic Press, New York, N.Y., 1971, p 271.
(14) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).